

**ISSUES IN MEDICINE****Cell-based therapy – navigating troubled waters**

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Cells and engineered tissue can be used to treat an increasing number of diseases. This development, together with promising pre-clinical data in regenerative medicine, has raised the expectations of many patients. However, this situation tends to make people vulnerable to the lures of companies that abuse the stem cell promise. The problem is compounded by people's propensity to believe that the healing powers of positive thinking, large sums of money and foreign institutions are greater than those of therapies developed through well-tested, properly constructed clinical trials.

Stem cell therapy has been proposed for many diseases, including diseases of the central nervous system (spinal cord injury, Alzheimer's disease, Parkinson's disease, cerebral palsy, multiple sclerosis), diabetes and heart disease (post-myocardial infarction, cardiac failure). Several clinical trials have shown an improvement in left ventricular ejection fraction in patients with cardiac disease, following stem cell administration (intra-coronary or intramyocardial). However, for most of the other diseases mentioned, there are no firm clinical data to justify the routine use of stem cells for their treatment.

Cell-based therapy, however, has been used very successfully in a few settings. The most universally accepted form of cell therapy is bone marrow transplantation (BMT), which has been practised for more than 50 years. Most of its indications have been repeatedly tested and verified through rigorously controlled clinical trials. Other currently applied forms of cell-based therapy include treating burns, dermal and corneal wounds, and orthopaedic problems.

**Questionable practices**

The global emergence of centres that purport to treat many human diseases using stem cells has generated confusion in the health care market. Many of these centres operate on the following basis:

- emotionally vulnerable patients are lured into a clinic, often via a website that promises miraculous cures for a large number of diseases
- clever marketing and careful evasion of the truth often underlie their immediate and superficial appeal

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- anecdotal evidence is provided, indicating how patients with similar diseases have been cured, often contrary to their medical practitioners' predictions (e.g. X was only given 3 months to live – and look at him now!)
- patients (or their parents) are charged excessively for these procedures, and must also cover the cost of travel and accommodation at sites that are frequently far from their homes
- no sound clinical data support these treatments, and repeated requests for data are usually either ignored or anecdotal evidence or a variety of disclaimers are provided, including the fact that the success of the treatment cannot be guaranteed.

Some companies are conducting 'clinical trials' that appear to be phase I in nature. However, the fact that there have (apparently) been no significant adverse reactions to the delivered products does not imply that a therapeutic effect has been attained. Any therapeutic effect would have to be specifically demonstrated. While the cells that are administered by these companies may do no harm, their healing properties still need to be demonstrated. Expensive treatments cannot simply be administered on the basis that they do no harm. Furthermore, the psychological impact of these therapies and the resulting placebo effect should not be underestimated, particularly when patients who pay large sums of money for novel forms of therapy strongly believe that their ailments will be healed. Inevitably, however, disappointment sets in as the placebo effect wears off.

The use of cells the side-effects of which have not been adequately studied could also have serious consequences. It appears that the less differentiated and more pluripotent the cells used for treatment, the greater is the probability that they will undergo malignant transformation. A dramatic example was a young boy who developed a multi-focal brain tumour following intracerebellar and intrathecal injection of human fetal neural stem cells for ataxia telangiectasia.<sup>1</sup> After three treatments (at ages 9, 10 and 12) at a clinic in Russia, he developed headaches caused by tumours at the sites of injection, which were found to have originated from the injected cells. At surgical removal, several satellite tumours were also found. The safety profile of the injected cells had not been adequately tested prior to administration, and there were no experimental/pre-clinical or clinical data to suggest that stem cells might be of benefit in ataxia telangiectasia.<sup>2</sup>

Another bedevilling issue is whether patients in these settings should pay for their treatments, which are essentially experimental in nature and could be seen as a form of clinical trial. In the absence of specific legislation, a case can be made for charging patients for routine blood and urine tests (several are required on the abovementioned websites). Ethically, however, it is highly questionable whether patients should

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be made to pay for treatments which have no, or limited, proven clinical benefit. Large sums of money change hands in these settings, and there are currently no universally agreed upon fee structures for the treatments. The vulnerability and determination of the affected individuals are indicated by the lengths to which they will go to raise the money needed, often to the detriment of close family members.

In response to these issues, scientists and health professionals around the world have published comments and guidelines on what should be considered ethical and fair in cell-based therapy.<sup>2-7</sup> In 2008, the International Society for Stem Cell Research published Guidelines for the Clinical Translation of Stem Cells (available at [http://www.isscr.org/clinical\\_trans](http://www.isscr.org/clinical_trans)), which 'provides a framework for the responsible and timely development of clinically useful stem-cell-based therapies'.<sup>8</sup> Furthermore, several papers published in *Nature Reports Stem Cells* severely criticised the growing commercial exploitation of patients through the use of untested and unproven so-called 'stem cell therapies'.<sup>9-12</sup> These reports emphasise the same critical point, that it is immoral and unethical to propose 'stem cell therapy' to patients if objective clinical improvement in a well-structured, documented, and approved clinical trial is not provided.

South Africa has not been spared these questionable practices, and the legal process against an alleged international stem cell scam (in which stem cells were offered to paralysed and terminally ill patients across Europe and the USA) appears to have stalled on technicalities.<sup>13</sup> We must ensure that South Africa does not allow the unethical administration of untested 'stem cell therapies' to emotionally vulnerable patients desperate for a cure. We can only become part of the global cell therapy fraternity on the basis of clinically proven stem cell therapies, currently limited to bone marrow transplantation (BMT), wounds/ulcers and orthopaedic conditions.

## The legislative vacuum in South Africa

Chapter 8 of the National Health Act (the major part of the legislation in South Africa that deals with the issue of cell-based therapy) has not been promulgated. This is a serious hiatus, since we have to rely on the outdated Human Tissue Act of 1983 to provide the necessary legislation. To compound the problem, the legislation in Chapter 8 is confusing and incomplete. The situation is attractive for companies wishing to set up cell-based therapy activities, as it creates an opportunity to establish therapies that might have been prevented by more comprehensive and restrictive legislation. However, the following should be borne in mind:

- Chapter 8 is being revised, and regulations will provide clear guidelines on what is permissible and what is not.

Companies may not need to deal with this now, but it will become a reality when the legislation comes into force. A defined time interval will allow companies to comply with the new legislation.

- Any form of therapy that is not established or that is experimental in nature will require the blessing of the Medicines Control Council (or its revised equivalent) before it can be administered.
- All clinical trials will have to be scrutinised by an ethics committee.

## Conclusion

Although there is unquestionable benefit to be derived from cell-based therapy, most of this (with the exception of BMT) still lies in the future, i.e. it is not part of the current reality of stem cells but rather in the realm of the still unproven, but nonetheless hope-generating, future promise. Urgent attention is being given to regulatory matters in cell therapy and all areas that fall under the umbrella of human tissues. Until this legislation is in place, health professionals should be aware of the questionable nature of the current treatments being offered to patients, and advise them appropriately to prevent disappointment, unwanted side-effects and unnecessary expense.

We certainly can envisage a world in which the promise of stem cells will be realised. Hope is a powerful tool in the maintenance of physical, emotional and spiritual health; but we should also strive to maintain a balance between reality and fantasy. If we allow the one to spill over into the other, we render ourselves vulnerable to the seductive lure of unscrupulous, dishonest and unethical practices.

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